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Serial No. : **10/820,904**
Filed : **April 8, 2004**
Title : **New Isoquinoline compounds**
Art. Unit. : **1625**
Examiner : **Z. N. DAVIS**

**HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C 20231**

Declaration under 37 CFR 1.132

I, Philippe DELAGRANGE, a citizen of France, of 23, rue Victor Hugo, 92130 Issy les Moulineaux, France, declare and say that :

I hold the degree of Doctor of University from the University Pierre et Marie Curie of Paris in 1990.

In 1991, I was appointed as Scientific Study Manager in Servier International Research Institute and Head of Pharmacological Projects in 1995 in Melatonin field.

I am the author or co-author of 29 patents and 80 international publications, the majority of which are devoted to the melatonin pharmacology.

I am one the co-inventors of U.S. Patent Application serial No. 10/820,904 filed April 8, 2004 concerning "New Isoquinoline compounds".

I am thoroughly familiar with the above-mentioned patent application and fully support the pharmacological experiments contained therein which were performed either by me or under my supervision. I also fully support the conclusions derived and the arguments presented as concerns the potential therapeutic interest of the compounds described.

The purpose of the present invention is to provide compounds having an activity on the melatonin receptors. The melatonin receptors are known to be divided in subtypes and the compounds of the invention have a very good melatonin receptor binding affinity. Because of this affinity, the compounds of the present invention are candidates for the treatment of disorders in which the melatoninergetic system is involved.

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Melatonin is a neurohormone synthesized by the pineal gland and then released in the blood which allows melatonin to be active both at the periphery and at the central levels where the melatonin receptors are present. A review of the distribution of melatonin receptor subtypes in tissues and some of their physiological effects has been recently published (Drugs of the Future, 2000, 25(9),pp 945-957).

For example, at the periphery, melatonin receptors have been reported on different arteries (Society for Neuroscience, 1996, 22, N°651.19, p. 1400) and in platelets (J. Pineal Res., 1992, 13, pp 60-65) and melatonin has been reported to have beneficial cardiovascular effects in human (J. Pineal Res., 1997, 22, pp 16-19), and potential clinical application in the treatment of myocardial ischemia (Life Sciences, 2000, 66(6), pp 503-509).

Melatonin binding sites have also been described on adipose tissues (Endocrinology, 2001, 142(10), pp 4264-4271) and phototherapy which affects the melatonin production

has been reported as effective for treatment of obesity (International Journal of Eating Disorders, 1996, 20(4), pp 443-446).

Moreover, abnormalities of the circadian rhythm of melatonin hormones have been described in eating disorders both in obese women or women with anorexia nervosa (Biol. Psychiatry, 1990, 27, pp 1007-1020).

Concerning the central nervous system, the melatonin receptors have been identified in many structures such as cerebellum, cortex, thalamus, hippocampus (Molecular Brain Research, 1996, 39, pp 117-126) and many studies have reported either effects of melatonin treatments or abnormal melatonin concentrations in different pathological disorders such as sleep disorders, jet lag, major depression and associated disorders, seasonal affective disorders, eating disorders (CNS Drugs, 1995, 3(3), pp 209-226; Psychopharmacology, 1990, 100, pp 222-226), Alzheimer's disease (Brain Research, 1990, 528, pp 170-174), schizophrenia (Schizophrenia Research, 1992, 7, pp 77-84), panic disorder (Journal of Affective Disorders, 1987, 12, pp 203-206), Parkinson's disease (J. Neurosurg., 1985, 63, pp 321-341), melancholia (Medical Hypotheses, 1988, 27, pp 271-276), chronic mild stress (Behavioural Pharmacology, 1999, 10, pp 73-83). MT₁ and/or MT₂ receptors are involved in the regulation of emotional responsiveness (Neuropharmacology, 2000, 39, pp 1865-71) and epilepsy (Exp. Brain Res., 1995, 107, pp 321-325).

In addition, melatonin may potentially provide prophylaxis or therapy for pathologies associated with aging (Endocrinology, 1999, 140(2), pp 1009-1012; Medical Hypotheses, 1991, 34, pp 300-309) and in diabetes (Clinical Endocrinology, 1986, 24, pp 359-364). Melatonin receptors have been identified in the digestive system, and studies suggest a beneficial role of melatonin on the digestive system (Current Pharmaceutical Design, 2001, 7, pp 909-931).

Melatonin has also been reported to play a role in ovulation and reproduction (Science, 1985, 227, pp 714-720; Rec. Med. Vet., 1991, 167(3/4), pp 227-239), to have an immunoregulatory and analgesic action (Drug Development Research, 1996, 39, pp 167-

173) and a beneficial action on the cerebral circulation (Am. J. Physiol., 1998, 275, pp 139-144).

Melatonin receptors have also been characterized in some brain blood vessels and in the choroid plexuses (Neuroscience, 1993, 52(2), pp 459-468) which indicated that melatonin analogues will be useful for treatment of migraine or cluster headache (Cephalalgia, 1996, 16, pp 494-496; Cephalalgia, 1995, 15, pp 136-139).

Lastly, the presence of melatonin receptors on different human cancerous tissues (Eur. J. of Pharmacology, 1993, 246, pp 89-96; Journal of clinical Endocrinology and Metabolism, 1996, 81(4), pp 1336-1342) and the positive clinical trials with melatonin (British Journal of Cancer, 1996, 74, pp 1466-1468) show the potential therapeutic of melatonin analogues as anticancer drugs.

In light of these papers, it is clear that the high selectivity for melatonin receptors is connected with a definite and positive utility of the compounds of the present invention in the treatment of the diseases and disorders which are recited in page 10 of the specification.

In light of these papers and according to the binding activity on the melatonin receptor subtypes I fully support the arguments presented as concerns the potential therapeutic interest in and utility of the compounds described.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under section 1001 of title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Further declarant sayeth not



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Executed at : Courbevoie .

Date : September 4, 2006

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